# Researchers identify and characterize three molecular subtypes of Alzheimer's

7 January 2021

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Researchers at the Icahn School of Medicine at Mount Sinai have identified three major molecular subtypes of Alzheimer's disease (AD) using data from RNA sequencing. The study advances our understanding of the mechanisms of AD and could pave the way for developing novel, personalized therapeutics.

The work was funded by the National Institute on Aging, part of the National Institutes of Health (NIH), and published in *Science Advances* on January 6, 2021.

RNA is a genetic molecule similar to DNA that encodes the instructions for making proteins. RNA sequencing is a technology that reveals the presence and quantity of RNA in a biological sample such as a brain slice.

Alzheimer's disease is the most common form of dementia, but it is quite diverse in its biological and pathological manifestations. There is growing evidence that disease progression and responses to interventions differ significantly among Alzheimer's patients. Some patients have slow cognitive decline while others decline rapidly; some have significant memory loss and an inability to remember new information while others do not; and some patients experience psychosis and/or depression associated with AD while others do not.

"Such differences strongly suggest there are subtypes of AD with different biological and molecular factors driving disease progression," said Bin Zhang, Ph.D., the lead author of the study, Director of the Center for Transformative Disease Modeling, and Professor of Genetics and Genomic Sciences at the Icahn School of Medicine.

To identify the molecular subtypes of AD, the researchers used a computational biology approach to illuminate the relationships among different types of RNA, clinical and pathological traits, and other biological factors that potentially drive the disease's progress. The research team analyzed RNA-sequencing data of more than 1,500 samples across five brain regions from hundreds of deceased patients with AD and normal controls, and identified three major molecular subtypes of AD. These AD subtypes were independent of age and disease stage, and were replicated across multiple brain regions in two cohort studies.

These subtypes correspond to different combinations of multiple dysregulated biological pathways leading to brain degeneration. Tau neurofibrillary tangle and amyloid-beta plaque, two neuropathological hallmarks of AD, are significantly increased only in certain subtypes.

Many recent studies have shown that an elevated immune response may help cause Alzheimer's. However, more than half of AD brains don't show increased immune response compared to normal healthy brains. The analysis further revealed subtype-specific molecular drivers in AD progression in these samples. The research also identified the correspondence between these molecular subtypes and the existing AD animal

models used for mechanistic studies and for testing candidate therapeutics, which may partially explain why a vast majority of drugs that succeeded in certain mouse models failed in human AD trials, which likely had participants belonging to different molecular subtypes.

Although the subtyping described by the researchers was performed post mortem using the patients' brain tissue, the researchers said that if the findings were validated by future studies, they could lead to the identification in living patients of biomarkers and clinical features associated with these molecular subtypes and earlier diagnosis and intervention.

"Our systematic identification and characterization of the robust molecular subtypes of AD reveal many new signaling pathways dysregulated in AD and pinpoint new targets," said Dr. Zhang, "These findings lay down a foundation for determining more effective biomarkers for early prediction of AD, studying causal mechanisms of AD, developing next-generation therapeutics for AD and designing more effective and targeted clinical trials, ultimately leading to precision medicine for AD. The remaining challenges for future research include replication of the findings in larger cohorts, validation of subtype specific targets and mechanisms, identification of peripheral biomarkers and clinical features associated with these molecular subtypes."

The AD subtyping study is supported by the NIH National Institute on Aging (NIA) and is part of the NIA-led Accelerating Medicines Partnership—Alzheimer's Disease (AMP-AD) Target Discovery and Preclinical Validation program. This public private partnership aims to shorten the time between the discovery of potential drug targets and the development of new drugs for Alzheimer's disease treatment and prevention.

**More information:** Ryan A. Neff et al, Molecular subtyping of Alzheimer's disease using RNA sequencing data reveals novel mechanisms and targets, *Science Advances* (2021). DOI: 10.1126/sciadv.abb5398

Provided by The Mount Sinai Hospital